REMARKS/ARGUMENTS

Claims 58-66 and 68-70 are pending in this application.

Claims 58-62 have been amended to remove the recitation of the phrase "native sequence." No new matter is added by this amendment to the claims. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

I. Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 58-62 and 69-70 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for the recitation of a "native sequence" polypeptide. The Examiner asserts that "it is not clear how one of ordinary skill in the art would be able to determine if a sequence is 'a native sequence' or not by looking at it." (Page 3 of the instant Office Action).

Without acquiescing to the PTO's arguments and solely in order to expedite prosecution of the instant application, Claims 58-62 have been amended to remove the recitation of the phrase "native sequence." Accordingly, withdrawal of the rejection under 35 U.S.C. §112, second paragraph is respectfully requested.

II. Claim Rejections Under 35 U.S.C. §§101 and 112, First Paragraph (Enablement)

Claims 58-66 and 68-70 remain rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." (Page 3 of the instant Office Action).

Claims 58-66 and 68-70 remain further rejected under 35 U.S.C. §112, first paragraph, allegedly because "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention." (Page 14 of the instant Office Action).

For the reasons outlined below, Applicants respectfully disagree and traverse the rejection. With respect to Claims 58-66 and 68-70, Applicants submit that not only has the Patent Office not established a *prima facie* case for lack of utility and enablement, but that the

PRO274 polypeptides possess a credible, specific and substantial asserted utility and are fully enabled.

First of all, Applicants respectfully maintain the position that the specification discloses at least one credible, substantial and specific asserted utility for the PRO274 polypeptides for the reasons previously set forth in Applicants' responses filed on November 18, 2004, and April 8, 2005.

Furthermore, as discussed in Applicants' Response of November 18, 2004, Applicants rely on the gene amplification data for patentable utility of the claimed the PRO274 polypeptide, and the gene amplification data for the gene encoding the PRO274 polypeptide is clearly disclosed in the instant specification under Example 114. As previously discussed, a ΔCt value of at least 1.0 was observed for PRO274 in at least three of the lung tumors listed in Table 9. Table 9 teaches that the nucleic acids encoding PRO274 showed approximately 1.00-1.61 ΔCt units which corresponds to $2^{1.00}$ -$2^{1.61}$ fold amplification or 2.0 fold to 3.05-fold amplification in three types of human primary lung tumors, LT4, LT16, and LT18. Accordingly, the present specification clearly discloses strong evidence that the gene encoding the PRO274 polypeptide is significantly amplified in a significant number of lung tumors.

The Examiner asserts that "the specification shows a very small increase in DNA copy number, approximately 2-3 fold, in a few tumor samples for PRO274." (Page 5 of the instant Office Action).

Applicants respectfully submit that the Examiner seems to have applied a heightened utility standard in this instance, which is legally incorrect. Applicants have shown that the gene encoding PRO274 demonstrated significant amplification, from 2 to 3.05 fold, in three lung tumors. As explained in the Declaration of Dr. Audrey Goddard (submitted with the Response filed November 18, 2004):

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample **is significant** and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique

as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. (Emphasis added).

By referring to the 2 -fold to 3.05-fold amplification of the PRO274 gene in lung tumors as "very small," the Examiner appears to ignore the teachings within an expert's declaration without any basis, or without presenting any evidence to the contrary. Applicants respectfully draw the Board's attention to the Utility Examination Guidelines (Part IIB, 66 Fed. Reg. 1098 (2001)) which state that:

> "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered".

Thus, given the absence of any evidence to the contrary, Appellants maintain that the 2.0 to 3.05-fold amplification disclosed for the PRO274 gene is significant and forms the basis for the utility claimed herein.

Further, Applicants respectfully submit that the amplification of PRO274 in even one lung tumor provides specific and substantial utility for PRO274 as a diagnostic marker of the type of lung tumor in which it was amplified. Applicants submit that the lung tumors listed in Table 9 are not similar tumors from different patients, but various types/classes of lung tumors at different stages. Accordingly, a positive result from one tumor, where the nucleic acid was amplified, but not from other tumors, indicates that the nucleic acid can be used as a marker for diagnosing the presence of that kind of tumor in which it was amplified. Amplification of the nucleic acid would be indicative of that specific class of lung tumor, whereas absence of amplification would be non-conclusive.

The Examiner asserts that the gene amplification data is not sufficient to demonstrate utility for the PRO274 polypeptides because "it is not predictable that gene amplification results in increased mRNA expression, or that increased mRNA expression results in increased protein production." (Page 4 of the instant Office Action). In support of this assertion, the Examiner has previously cited references by Pennica *et al.* and Gygi *et al.* The Examiner asserts that Pennica *et al.* was cited as "evidence showing a lack of correlation between gene (DNA) amplification and

elevated mRNA levels." (Page 5 of the instant Office Action). Applicants respectfully submit that, for the reasons previously set forth in the Applicants' response filed on November 8, 2004, the teachings of Pennica *et al.* are specific to *WISP* genes, and say nothing about the correlation of gene amplification and protein expression in general. The Examiner asserts that Gygi *et al.* was cited "as providing evidence that polypeptide levels cannot be accurately predicted from mRNA levels, and that variances as much as 40-fold or 50-fold were not uncommon." (Pages 5-6 of the instant Office Action). Yet the Examiner acknowledges that "Gygi *et al.* demonstrates that high levels of mRNA generally correlate with high levels of protein and that it appears that there is a general positive correlation between mRNA levels and protein levels." (Page 6 of the instant Office Action). Thus Gygi *et al.* supports Applicants' position that there is a positive correlation between the overexpression of mRNA and protein.

The instant Office Action suggests that a "more relevant reference" is Chen *et al.* (Page 6 of the instant Office Action). Applicants respectfully submit that the analysis by Chen *et al.* is not applicable to the present application. The Examiner cites Chen *et al.* to the effect that only twenty-eight of the 165 protein spots (17%) or 21 of 98 genes (21.4%) had a statistically significant correlation between protein and mRNA expression data.

First, Applicants note that proteins selected for study by Chen *et al.* were those detectable by staining of 2D gels. As noted in, for example, Haynes *et al.* (Electrophoresis 19:1862-1871 (1998); copy enclosed) there are problems with selecting proteins detectable by 2D gels. "It is apparent that without prior enrichment only a relatively small and highly selected population of long-lived, highly expressed proteins is observed. There are many more proteins in a given cell which are not visualized by such methods. Frequently it is the low abundance proteins that execute key regulatory functions" (page 1870, col. 1). Thus Chen *et al.* by selecting proteins detectable by staining of 2D gels are likely to have excluded from their analysis many of the proteins most likely to be significant as cancer markers.

Secondly, Chen *et al.* looked at expression levels across a set of samples including a large number of tumor samples (76) along with a much smaller number of normal samples (9). The tumor samples were taken from stage 1 and stage III lung adenocarcinomas, which were

classified as bronchoaveolar, bronchial derived or both bronchial and bronchoaveolar derived. Accordingly, the tissues examined were from different tissues in different stages of normal or cancerous growth. The authors determined the relationship between mRNA and protein expression by using the average expression values for all samples. The average value for each protein or mRNA was generated using all 85 lung tissue samples. This resulted in negative normalized protein values in some cases. Further, the authors chose an arbitrary threshold of 0.115 for the correlation to be considered significant. Accordingly, the Chen paper does not account for different expression in different tissues or different stages of cancer.

Thirdly, no attempt was made to compare expression levels in normal versus tumor samples, and in fact the authors concede that they had too few normal samples for meaningful analysis (page 310, col. 2). As a result, the analysis in the Chen paper shows only that a number of randomly selected proteins have varying degrees of correlation between mRNA and protein expression levels within a set of different lung adenocarcinoma samples. The Chen paper does not address the issue of whether increased mRNA levels in the tumor samples taken together as one group, as compared to the normal samples as a group, correlated with increased protein levels in tumorous versus normal tissue. Accordingly, the results presented in the Chen paper are not applicable to the application at issue.

The correct test of utility is whether the utility is "more likely than not". In the case of the Chen reference, even if the analysis presented is correct (which is disputed), a review of the correlation coefficient data presented in the Chen *et al.* paper indicates that it is more likely than not that increased mRNA expression correlates with increased protein expression. A review of Table 1, which lists 66 genes [the paper incorrectly states there are 69 genes listed] for which only one protein isoform is expressed, shows that 40 genes out of 66 had a positive correlation between mRNA expression and protein expression. This clearly meets the test of "more likely than not". Similarly, in Table II , 30 genes with multiple isoforms [again the paper incorrectly states there are 29] were presented. In this case, for 22 genes out of 30, at least one isoform showed a positive correlation between mRNA expression and protein expression. Furthermore, 12 genes out of 29 showed a strong positive correlation [as determined by the authors] for at least

one isoform. No genes showed a significant negative correlation. It is not surprising that not all isoforms are positively correlated with mRNA expression. Certain isoforms are likely non-functional proteins. Thus, Table II also provides that it is more likely than not that protein levels will correlate with mRNA expression levels.

The same authors in Chen *et al.*, published a later paper, Beer *et al.*, Nature Medicine 8(8) 816-824 (2002) (copy enclosed) which described gene expression of genes in adenocarcinomas and compared that to protein expression. In this paper they report that " these results suggest that the oligonucleotide microarrays provided reliable measures of gene expression" (page 817). The authors also state "these studies indicate that many of the genes identified using gene expression profiles are likely relevant to lung adenocarcinoma". Clearly the authors of the Chen paper agree that microarrays provide a reliable measure of gene expression levels and can be used to identify genes whose overexpression is associated with tumors.

Similarly, the references previously submitted by Applicants (the Orntoft, Hyman, and Pollack references), also analyzed mRNA and protein expression levels for genes known to be amplified in tumor samples. These papers also indicate that it is more likely than not that increased gene expression levels correlate with increased expression of the protein. The Chen reference does not provide sufficient evidence to dispute this finding.

The Examiner further cites Anderson *et al.* to the effect that there was a poor correlation (0.48) between mRNA and protein levels in liver cells. Applicants submit that the teachings of Anderson *et al.* do not apply to the presently claimed invention because Anderson *et al.* studied mRNA/protein correlation in proteins obtained from liver tissue, while the present invention is directed to polypeptides that are overexpressed in lung tumor, which is an entirely different cellular environment from liver tissue. It would be apparent that different post-translational or post-transcriptional regulation mechanisms are involved in these two systems. Therefore, the conclusion of Anderson *et al.* does not apply to proteins associated with tumor tissues. Moreover, even the author in this reference admitted that several experimental flaws in this paper will limit that accuracy of the data. For instant, the protein measurements rely on CBB binding and its is well-known that different proteins can bind CBB with different affinities. More

significantly, the authors did not measure actual mRNA abundance for each protein, but looked at the numbers of clones found in a library. The precision of these measurements is limited because several proteins studied were represented only by one or two clones. As the authors admit, "such small numbers of clones lead to potentially large quantitative errors because of sampling error" (page 536, col. 1). As can be seen in Table 1, the data from the proteins represented only by one or two clones strongly affects the non-linearity of the total dataset. Thus these technique limitations are detrimental to the accuracy of the protein and mRNA abundance data as well as the conclusions based on these data. Finally, even assuming it is accurate, the conclusion by Anderson *et al.* does not support the Examiner's position. To the contrary, the data in Anderson *et al.* suggest that there is a significant correlation between mRNA and protein levels. Anderson *et al.* have observed a correlation coefficient of 0.48 between protein and mRNA abundance. As shown, for example, in Chen *et al.*, correlation coefficients over 0.25 are deemed to be significant (see Table II, and page 309, col. 1). In fact, the highest correlation coefficient reported by Chen *et al.* is 0.4003, less than the 0.48 observed for the Anderson *et al.* data. Accordingly, the Examiner cannot rely on the teaching of Anderson *et al.* to establish a *prima facie* showing of lack of utility.

Applicants reiterate that the evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant.

The Patent Office has failed to meet its initial burden of proof that Applicant's claims of utility are not substantial or credible. The arguments presented by the Examiner in combination with the Chen *et al.* and Anderson *et al.* papers do not provide sufficient reasons to doubt the statements by Applicants that PRO294 has utility. As set forth above, both Chen *et al.* and

Anderson *et al.* support Applicants' position that there is a positive correlation between the overexpression of mRNA and protein.

Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. First, the articles by Ornoft *et al.*, Hyman *et al.*, and Pollack *et al.*, (submitted with Applicants' response filed November 18, 2004) collectively teach that in general, gene amplification increases mRNA expression. Second, the Declaration of Dr. Paul Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, shows that, in general, there is a correlation between mRNA levels and polypeptide levels.

The Examiner asserts that "Ornoft *et al.* do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time.... Ornoft *et al.* concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p.40)."

Applicants respectfully point out that in Ornoft *et al.*, 1,800 genes that yielded an increase or decrease in mRNA expression in two invasive tumors compared to the two non-invasive papillomas were then mapped to chromosomal locations. The chromosomes had already been analyzed for amplification by hybridizing tumor DNA to normal metaphase chromosomes (CGH). Ornoft *et al.* used CGH alterations as the independent variable and estimated the frequency of expression alterations of the 1,800 genes in the chromosomal areas. Ornoft *et al* found that in general (77% and 80% concordance) areas with a strong gain of chromosomal material contained a cluster of genes having increased mRNA expression (see page 40). Ornoft *et al.* state, "For both tumors TCC733 ($p<0.015$) and TCC827 ($p<0.00003$) a highly significant correlation was observed between the level of CGH ratio change (reflecting the DNA copy number) and alterations detected by the array based technology" (see page 41, column 1). Ornoft *et al.*, also studied the relation between altered mRNA and protein levels using 2D-PAGE analysis. Ornoft *et al.* state, "In general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations.... 26 well focused proteins whose genes had

a known chromosomal location were detected in TCCs 733 and 335, and of these 19 correlated ($p<0.005$) with the mRNA changes detected using the arrays." (See page 42, column 2 to page 34, column 2). Accordingly, Ornoft *et al.* clearly support Applicants' position that proteins expressed by genes that are amplified in tumors are useful as cancer markers. Applicants further note that the analyses performed by Hyman *et al.* and Pollack *et al.* were both on a gene-by gene basis, and clearly show that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

The Examiner next asserts that "none of the three papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics" (Page 9 of the instant Office Action). Applicants respectfully point out that Hyman *et al.* conducted additional studies of one of the genes found to be amplified, HOXB7, and found **"a clinical association between HOXB7 amplification and poor patient prognosis."** (Page 6244, col.1 to col.2; emphasis added). Thus the results of Hyman *et al.* confirm that genes which are amplified in tumors have prognostic utility. The Examiner's attention is also respectfully directed to the final paragraph of Pollack *et al.*, wherein the authors conclude that "a substantial portion of the phenotypic uniqueness (and, by extension, the heterogeneity in clinical behavior) among patients' tumors may be traceable to underlying variation in DNA copy number." (Page 12698, col. 2). Accordingly, Pollack *et al.* confirm that genes that are amplified in at least one type of tumor are useful as markers for that type of tumor, and for prognostic uses directed to that type of tumor.

The Examiner further asserts that "[b]ecause Ornoft *et al.* only looked at a small sample of abundant proteins, it is not predictive that a small increase in transcript will result in increased protein abundance in general." (Page 8 of the instant Office Action). The Examiner also notes that Hyman *et al.* and Pollack *et al.* did not investigate polypeptide levels. Applicants submit that the articles by Ornoft *et al.*, Hyman *et al.*, and Pollack *et al.* were submitted primarily as evidence that in general, gene amplification increases mRNA expression. As evidence that, in general, there is a correlation between mRNA levels and polypeptide levels, Applicants further submitted the Declaration of Dr. Paul Polakis. Thus Applicants do not rely upon the Ornoft *et*

al., Hyman *et al.*, and Pollack *et al.* articles to show a correlation between mRNA levels and polypeptide levels, because such a correlation is demonstrated in the Polakis Declaration.

As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To the date of the Polakis Declaration, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested according to the Polakis Declaration greatly exceed this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

With respect to the Polakis Declaration, the Examiner asserts that "[o]nly transcripts that are present in tumor cells at significantly higher levels than in corresponding normal human cells were analyzed, which from the art would more likely result in increased protein abundance." (Page 11 of the instant Office Action). Applicants respectfully point out that Applicants have already shown that, as evidenced by the Goddard Declaration, the gene encoding PRO274 showed <u>significant</u> amplification in lung tumors as compared to normal tissues. As discussed above, the art demonstrates that gene amplification is associated with increased mRNA levels. Accordingly, PRO274 mRNA levels would also be expected to be significantly increased in

tumor cells. Thus PRO274 belongs to exactly that class of molecules experimentally demonstrated, according to both the Polakis Declaration and the cited art, to "most likely result in increased protein abundance."

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between DNA, mRNA, and polypeptide levels, these instances are exceptions rather than the rule. In the majority of amplified genes, as exemplified by Orntoft *et al.,* Hyman *et al.,* Pollack *et al.,* and the Polakis Declaration, the teachings in the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO274 gene, that the PRO274 polypeptide is concomitantly overexpressed. Thus, the claimed PRO274 polypeptides have utility in the diagnosis of cancer.

Even if there is no correlation between gene amplification and increased mRNA/protein expression, (which Applicants expressly do not concede), a polypeptide encoded by a gene that is amplified in cancer would still have a specific, substantial, and credible utility. As evidenced by the Ashkenazi Declaration and the teachings of Hanna and Mornin (submitted with Applicants' Response filed November 18, 2004), simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy for the tumor as demonstrated by the real-world example of the breast cancer marker HER-2/neu.

Applicants have clearly shown that the gene encoding the PRO274 polypeptide is amplified in at least three lung tumors. Therefore, the PRO274 gene, similar to the HER-2/neu gene disclosed in Hanna *et al.*, is a tumor associated gene. Furthermore, as discussed above, in the majority of amplified genes, the teachings in the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO274 gene, that the PRO274 polypeptide is concomitantly overexpressed.

However, even if gene amplification does not result in overexpression of the gene product (*i.e.*, the protein) an analysis of the expression of the protein is useful in determining the course of treatment, as supported by the Ashkenazi Declaration and the Hanna article. The Examiner asserts that "[i]t has not been demonstrated that the protein of the instant invention is differentially expressed in different tumors" and that "the mere assertion that it may be differentially expressed does not provide a specific and substantial utility, and is an invitation to experiment." (Page 13 of the instant Office Action). The Examiner appears to view the testing described in the Ashkenazi Declaration and the Hanna article as experiments involving further characterization of the PRO274 polypeptide itself. In fact, such testing is for the purpose of characterizing not the PRO274 polypeptide, but the tumors in which the gene encoding PRO1555 is amplified. The PRO274 polypeptide is therefore useful in tumor categorization, the results of which become an important tool in the hands of a physician enabling the selection of a treatment modality that holds the most promise for the successful treatment of a patient.

Accordingly, Applicants submit that when the proper legal standard is applied, one should reach the conclusion that the present application discloses at least one patentable utility for the PRO274 polypeptides. Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed PRO274 polypeptides, for example, in the diagnosis of cancer.

Accordingly, withdrawal of the rejections of Claims 58-66 and 68-70 under 35 U.S.C. §101 and §112, first paragraph, is respectfully requested.

III. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 58-62 and 69 and 70 remain rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking adequate written description for the claimed variant polypeptides having at least 80-99% identity to SEQ ID NO:7.

The Examiner states that "the only factors present in the claim are functional, in that the protein of SEQ ID NO:7 is encoded by a nucleic acid that is amplified in lung cancer." The Examiner further alleges, "It is clear that while there *could* be additional polypeptides that meet

the limitations of the claims, that conception of such polypeptides has not occurred, and cannot occur until their actual isolation, as it is not predictable what additional mutations in SEQ ID NO:7 would occur in nature and further be associated with lung cancer." (Page 15 of the instant Office Action).

Applicants respectfully submit that the instant specification evidences the actual reduction to practice of a full-length PRO274 polypeptide of SEQ ID NO:7, with or without its signal sequence. The Examiner has acknowledged that polypeptides comprising the sequence set forth in SEQ ID NO:7 meet the written description provision of 35 U.S.C. §112, first paragraph. Thus, the genus of native sequence polypeptides with at least 80% sequence identity to SEQ ID NO:7, which possess the functional property of having a nucleic acid which is amplified in lung tumors would meet the requirement of 35 U.S.C. §112, first paragraph, as providing adequate written description.

Applicants have provided native PRO sequence SEQ ID NO:7. The present application also describes methods for identifying genes which are amplified in lung cancer. Example 114 of the present application provides step-by-step guidelines and protocols for the gene amplification assay. By following the disclosure in the specification, one skilled in the art can easily test whether a gene encoding a native variant PRO274 protein is amplified in lung tumors.

The specification further describes methods for the determination of percent identity between two amino acid sequences. (See page 122, line 34 to page 125, line 37). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 180, line 10, to page 183, line 8). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 182). Accordingly, one of skill in the art could identify whether the variant PRO274 native sequence falls within the parameters of the claimed invention. Once such an amino acid sequence was identified, the specifications sets forth methods for making the amino acid sequences (see page

180, line 9 to page 184, line 35) and methods of preparing the PRO polypeptides (see page 185, line 36 and onward).

Therefore, Applicants respectfully submit that one of skill in the art could readily test a nucleic acid sequence which encodes the variant polypeptide to determine whether it is amplified by the methods set forth in Example 114.

"An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."[1] As discussed above, Applicants have recited structural features, namely, 80% sequence identity to the amino acid sequence SEQ ID NO:7, which are common to the genus. Applicants have also provided guidance as to how to make the recited polypeptide variants of SEQ ID NO:7, including listings of exemplary and preferred sequence substitutions. The genus of claimed polypeptides is further defined by having a specific functional activity for the encoding nucleic acid, of being amplified in lung tumors. Accordingly, a description of the claimed genus has been achieved.

The Examiner's attention is respectfully directed to Example 14 of the Synopsis of Application of Written Description Guidelines issued by the U.S. Patent Office, which clearly states that protein variants meet the requirements of 35 U.S.C. §112, first paragraph, as providing adequate written description for the claimed invention even if the specification contemplates but does not exemplify variants of the protein if (1) the procedures for making such variant proteins are routine in the art, (2) the specification provides an assay for detecting the functional activity of the protein and (3) the variant proteins possess the specified functional activity and at least 95% sequence identity to the reference sequence.

As discussed above, the procedures for making the claimed variant proteins are well known in the art and described in the specification. The specification also provides an assay,

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[1] M.P.E.P. §2163 II(A)(3)(a)

shown in Example 114, for detecting the recited functional activity of the variant polypeptides. Finally, the claimed variant proteins possess both the specified functional activity and a defined degree of sequence identity to the reference sequence, SEQ ID NO:7. Accordingly, the recited polypeptide variants meet the standards set forth in the Written Description Guidelines.

Withdrawal of the written description rejection of Claims 58-62 and 69-70 under 35 U.S.C. §112, first paragraph, is therefore respectfully requested.

IV. Claim Rejections Under 35 U.S.C. §102 and 35 U.S.C. §103

Claims 58-66 and 68 remain rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Ho *et al.*, Science, Vol. 289, pp 265-270 (publication date July 14, 2000).

Claims 69-70 further remain rejected under 35 U.S.C. §103(a) as being unpatentable over Ho *et al.* in view of Hopp *et al.*, U.S. Patent No. 5,011,912.

These rejections are based upon an effective filing date for the application of October 15, 2001, the actual filing date of the instant application.

As discussed previously in the Applicants' responses filed on November 18, 2004 and April 8, 2005, Applicants rely on the gene amplification assay (Example 114) for patentable utility which was first disclosed in International Application No. PCT/US00/03565, filed February 11, 2000, priority to which has been claimed in this application. Applicants respectfully maintain the position that that the specification provides the support required to establish utility for the claimed protein, for example, in the diagnosis of cancer, for the reasons set forth in Applicants' responses filed on November 18, 2004 and April 8, 2005, and above. Accordingly, Applicants submit that the subject matter of the instant claims is supported by the disclosure in International Application No. PCT/US00/03565. Therefore, the effective filing date of this application is February 11, 2000, the filing date of International Application No. PCT/US00/03565.

As discussed above, the pending claims of the instant application are entitled to the effective filing date of February 11, 2000, and hence, Ho *et al.* is not prior art under 102(b) since its publication date is after the effective priority date of this application. Since the primary

reference, Ho *et al.* is not prior art, Applicants respectfully submit that the instant claims are not obvious over Ho *et al.* in view of Hopp *et al.* Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejections under 35 U.S.C. §§102 and 103.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2630 P1C8**).

Respectfully submitted,

Date: October 28, 2005

By: _____
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